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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/030,351
Filing Date: June 07, 2002
Appellant(s): LINDSAY ET AL.

Paul T. Cark
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 03/05/2009 appealing from the Office action mailed 01/30/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

USPN 5,633,075	DeBoer	5-1997
USPN 5,322,775	Clark	6-1994
USPN 5,831,141	Lubon	11-1998

Morinaga *et al* (1983, PNAS, 80:4604-4608)

Bennett *et al* (1997, Breast Cancer Research and Treatment, 45:169-179)

Al-Awqati *et al.*, 1978, Clin Chim Acta, 89:173-182

Chaturvedi *et al.*, 1998, Prep Biochem Biotechnol, 28:293-303

Parker *et al*, 2004, Protein Expression and Purification, 38:177-183

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1,6-7 and 21-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeBoer (1997, US 5,633,076; IDS) *or* Clark (1994, US 5,322,775;IDS) *or* Lubon (1998, US 5,831,141; IDS) in view of Morinaga (1983, PNAS, Vol. 80, pages 4604-4608; IDS) and Bennett (1997, Breast Cancer Research and Treatment, Vol. 45, pages 169-179; IDS).

Claim 1 is drawn to a nucleic acid encoding rHuAFP operably linked to a milk-specific promoter and a leader sequence encoding a protein secretory signal. Claim 25 requires said nucleic acid sequence encode a non-glycosylated form of rHuAFP.

Claim 6 is drawn to milk of a non-human mammal comprising biologically active rHuAFP. Claim 7 is drawn to the milk of claim 6 wherein the milk is produced by a non-human transgenic mammal whose genome comprises the transgene recited in claim 1 and claim 26 limits the milk to that made from the mammal wherein the transgene comprises a nucleic acid encoding a non-glycosylated form of rHuAFP.

Claim 21 is drawn to a non-human transgenic mammal expressing biologically active rHuAFP in its milk wherein genome of the mammal contains a transgene encoding the nucleic acid as set forth in claim 1, enabling secretion of rHuAFP by the mammary epithelial cells of the mammal into the milk. Claim 27 is drawn to the same mammal wherein the rHuAFP is non-glycosylated. Claim 22 limits the species of mammal of claim 21 to a goat, cow, sheep or pig. Claim 23 is drawn to a method of preparing biologically active rHuAFP using the mammal of claim 21 and collecting the milk therefrom, while claim 24 adds an additional method step of purifying rHuAFP from said milk.

DeBoer taught generating transgenic cows and mice using transgenes encoding human serum albumin (see Example 10), human lactoferrin (see Example 5) or human lysozyme (see Example 22) operably linked to the αS1 casein promoter (see Example 5) or β lactoglobulin promoter, which are milk-specific promoters (see Example 20), and a signal sequence (see Examples 4 and 5 for hLF and Example 10 for hSA). The embryos were grown to generate mammals who later express the recombinant protein in the milk. DeBoer also taught purifying hSA from the milk (Example 11). Inherently, to purify or determine presence of a protein in milk, the milk must be collected as required by claim 23. The teachings of DeBoer include milk derived from the mammals as required by claims 6 and 7.

Similarly, Clark taught generating transgenic sheep and mice using a transgene encoding Factor IX operably linked to the β–lactoglobulin promoter, a milk-specific promoter, and a secretion signal sequence (col. 29, lines 23-44 and 50-5; col. 15, lines 29-31). The embryos were

grown to generate mammals that later express the recombinant protein in the milk (see Example 8). Clark also taught collecting (col. 19, lines 21-24) and purifying the protein from the milk (col. 19, lines 29-34). The teachings of Clark include milk derived from the mammals as required by claims 6 and 7.

Additionally, Lubon taught generating transgenic pigs and mice using a transgene encoding human protein C operably linked to the whey acid protein promoter, a milk-specific promoter, and secretion signal sequence (col. 11, lines 5-37; mouse, col. 12, lines 23-35; pig, col. 12, lines 37-64). The embryos were grown to generate mammals that later express the recombinant protein in the milk (for example see Example 11; Figure 7). Lubon also taught collecting and purifying the protein from the milk (col. 14, lines 8-20;col. 22, lines 35-44). The teachings of Lubon include milk derived from the mammals as required by claims 6 and 7.

Neither DeBoer, Clark nor Lubon taught human AFP as the protein being expressed in the mammary glands of the mammals.

However, Morinaga taught the nucleic acid sequence of AFP (see Figure 2).

Additionally, Bennett compared natural and recombinant human AFP made using *E. coli*. Bennett taught that the availability of large quantities of homogenous, biologically active recombinant human AFP would facilitate further study and therapeutic potential of the protein and that the recombinant and natural proteins were similar in all aspects evaluated.

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make the claimed transgenic mammals and milk derived therefrom as taught by each of DeBoer, Clark and Lubon wherein the gene expressed and secreted into the milk was the rHuAFP gene as taught by Morinaga. It would have been obvious to replace the various genes of each of DeBoer, Clark and Lubon with the rHuAFP gene, as expression of a transgene in the mammary gland was an art accepted means of producing large quantities of recombinant protein. One of ordinary skill in the art would have been sufficiently

motivated to produce large quantities of rHuAFP for use in cancer therapy as Bennett taught that recombinant human AFP can effectively bind estrogen and may be a regulator of estrogen-dependent human breast cancer (Abstract, last 3 lines; page 170, col. 1, paragraph 2).

The skilled artisan would have a reasonable expectation of success in combining the teachings of DeBoer, Clark or Lubon with those of Morinaga and Bennett because it was routine in the art to express a recombinant gene in the mammary epithelial cells of mammals and a vast array of genes had been utilized and expressed successfully.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

(10) Response to Argument

Appellant argues that the Examiner is using impermissible hindsight in that Morinaga provides the additional teaching and motivation to apply the methods of each of Deboer, Clark and Lubon to produce rHuAFP in the milk of mammals while Bennett supports a motivation to make rHuAFP in large quantities (page 7 of Brief).

In response to Appellant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Appellant fails to point out what hindsight was used in establishing obviousness of the claimed invention. Each of DeBoer, Clark and Lubon render obvious the use of the claimed mammalian system to make any recombinant protein with a reasonable expectation of success. Bennett provides evidence of motivation and desire to produce rHuAFP.

Thus, the prior art provides all the teachings, suggestion and motivation to render obvious the claimed invention and no hindsight reasoning is used.

Appellant also asserts that the Examiner has made a new rule that no one can be granted a patent on the expression of any protein in the milk of a transgenic animal (see page 7 of Brief). In response, the Examiner has made no such rule but has merely stated that it is obvious to make any protein of interest in the absence of evidence to the contrary. Such evidence would be that which specifically establishes nonobviousness at the time of filing. In the instant case, a multitude of proteins had been made by secretion into the milk of transgenic animals and the production of recombinant AFP from a variety of sources was known and recognized as useful.

Appellant argues that each of DeBoer, Clark and Lubon, despite listing many proteins to be expressed in the described system, fail to make mention of HuAFP (pages 8-9). Appellant argues that to remedy this deficiency, the office cites both Morinaga and Bennett. Appellant points out that Morinaga merely discloses the nucleic acid sequence of HuAFP but does not teach, suggest or provide motivation for the expression of rHuAFP in the milk of a mammal using a nucleic acid comprising a milk-specific promoter and a leader sequence in combination with a nucleic acid encoding HuAFP (page 9, Brief). Appellant argues that Bennett also fails to teach or suggest the expression and secretion of rHuAFP into the milk of a mammal.

In response, the components of the transgene necessary for milk-specific expression and secretion are taught by each of DeBoer, Clark and Lubon. Neither Morinaga nor Bennett are relied upon for these teachings. All components of the invention, with exception of the sequence of HuAFP, are met by each of DeBoer, Clark and Lubon and the rejection is based simply on a substitution of one known protein for another, given motivation provided by Bennett.

Appellant argues that publications available prior to Appellant's filing date direct the skilled artisan away from the expression of rHuAFP in milk (page 10, Brief). Appellant, relying on teachings of Vallette (1989, Biochim. Biophys. Acta 99:302-312), Haouruigi, (1992, Biochim. Biophys. Acta, 1125:157-165) and Parmelee (1978, J. Biol. Chem., 253:2114-2119), argues that unsaturated fatty acids were known to inhibit the activity of AFP as determined by detection of conformational changes that affect estrogen binding and immunoreactivity. Appellant argues that the inventors demonstrated that HuAFP secreted into the milk of a goat does bind fatty acids therein.

In response, the potential for binding or other natural interaction with some fatty acids in milk does not indicate that all, if any, properties of rHuAFP will be irreversibly affected by the levels of specific fatty acids that are present in milk and does not indicate that any such change would make the protein undesirable. After all, AFP binds fatty acids in its natural in vivo environment and binding of a fatty acid as a ligand would be considered a natural property of AFP. Vallette teaches that the identity and quantity of fatty acids present is important in predicting the inhibition of estrogen binding and thus, such a variability in the effect of various fatty acids on AFP would likely hold true for other activities of AFP. There is no evidence as to which, if any, activities of AFP would be altered by the identity and concentration fatty acids characteristic of milk. The study of Vallette consisted of an unnatural, in vitro situation of incubating AFP with free fatty acids. Neither Appellant nor Vallette provide a nexus between this study and what occurs in a more complex in vivo environment. Vallette does not provide any teachings relevant or specific to mammary epithelial cells and does not indicate that any activity of AFP would be affected in the milk. The in vivo physiology is vastly different from the in vitro environment used in Vallette and the interactions that the free fatty acids may have with other proteins, as well as with AFP, differ. Thus, Appellant has failed to provide any concrete or

specific evidence or expectation that the fatty acids present in milk would alter, in any significant, irreversible or undesirable manner, the usefulness of rHuAFP produced therein.

Similarly, Appellant refers to arguments previously presented in the Remarks dated 11/02/2007 at page 9, paragraph 1, that Haouriugi teaches that free fatty acids induce subtle, specific changes in the binding of hormones to plasma proteins, including AFP. This argument was and is not persuasive. The occurrence of subtle conformational changes observed in AFP in plasma and potentially induced by other, various conditions (i.e those of Vallette, above) did not preclude the isolation and usefulness of AFP from various sources with vastly different chemical environments ranging from *E. coli* and yeast, to amniotic fluid, liver, and human cord blood (see Al-Awqati *et al.*, 1978, Clin Chim Acta, 89:173-182; Chaturvedi *et al.*, 1998, Prep Biochem Biotechnol, 28:293-303). Thus, there is no indication what changes, if any, in the properties of AFP will occur when the AFP is produced in the mammary environment. In fact, rHuAFP appears identical when isolated from amniotic fluid in comparison to that isolated from fetal liver (see Al-Awqati, 1978) and coincidentally, rHuAFP appears identical when isolated from milk of a transgenic mammal as compared to natural AFP isolated from human cord blood (see Parker, 2004, of record, page 151, paragraph bridging columns). Appellant has stated that relying on Parker as evidence is impermissible hindsight (page 15, Brief). However, Parker is not relied upon for obviousness or predictability in combining the art of record. Rather, Parker is merely used to verify what was already known in the art-that post-translational processing of HuAFP is not necessary and that there appears to be no material differences between AFP isolated from a vast range of sources. Parker is not relied upon in support of the rejection of record.

Thus, it appears as though the characteristics of AFP may differ to some degree in any environment, however, these differences do not preclude its isolation and use from these various sources. Al-Awqati (1978) found slightly different properties for AFP isolated from fetal liver and amniotic fluid; however, these differences failed to alter the functionality of the resulting

proteins (see pages 180-181). Thus, the Examiner fails to find that any of Vallette, Haouriugi or Parmelee teach away from the instant invention.

Similarly, Appellant argues that there was no expectation of success in combining the references of either of DeBoer, Clark or Lubon with Morinaga and with Bennett (page 12, Brief). The basis of this unpredictability, according to Appellant lies, in part, in the presence of fatty acids in milk that can induce conformational changes that affect at least some of the biological activities of HuAFP (see above) and that in light of this knowledge, the skilled artisan would have no reasonable basis to conclude that expression of rHuAFP in the milk of a transgenic mammal would yield a biologically active protein. Appellant argues there is additional unpredictability associated with expressing rHuAFP as Lubon taught some amount of inactive recombinant protein may be made in the transgenic mammals used and refers to the lack of post-translational processing in mammary epithelial cells as a further level of unpredictability in obtaining an active rHuAFP protein (page 14, Brief).

In response, Appellant has only provided evidence demonstrating effects of some fatty acids on characteristics of HuAFP but has not raised significant doubt as to a reasonable expectation of success (see above). Appellant continues to doubt the potential success in combining the references by way of teachings relating to difficulties in obtaining protein C from milk of transgenic mammals (page 14, Brief). This difficulty, specific to Protein C, centers around the necessity of post-translational modification for protein C activity, which is not fully carried out by mammary epithelial cells. While the lack of post-translational modification of proteins in mammary epithelial cells are of concern in making some recombinant proteins in milk, this would *not* be the case for rHuAFP, which has been made in both *E.coli* and yeast and has been found to be active despite a lack of post-translational processing. Thus, Appellant's

arguments regarding the art teaching away from the combination of DeBoer, Clark or Lubon with Morinaga and Bennett and a lack of reasonable success are not persuasive.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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